Insights into the roles of the inflammatory mediators IL-1, IL-18 and PGE2 in obesity and insulin resistance

Olivia Osborn, Hermann Gram, Eric P. Zorrilla, Bruno Conti, Tamás Bartfai

The Harold L. Dorris Neurological Research Institute and Molecular and Integrative Neurosciences Department, The Scripps Research Institute, La Jolla, California, USA
Novartis Institutes for Biomedical Research, Basel, Switzerland
Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, California, USA

Summary

Body weight homeostasis is regulated by central and peripheral mechanisms, in which cytokines appear to have an important role. The circulating levels of the cytokines interleukin 1 (IL-1) and interleukin 18 (IL-18), and of inflammatory mediators such as prostaglandin E2 (PGE2), amongst others, are elevated in obese individuals. The low-grade inflammation associated with obesity may contribute to the development of insulin resistance, impaired glucose tolerance and type 2 diabetes. This review highlights results of studies in mice which indicate important roles for these proinflammatory cytokines during the development of obesity and insulin resistance, and in the treatment of type 2 diabetes.

Key words: obesity; insulin resistance; diabetes; inflammation; interleukin 1; IL-1; IL-1Ra; interleukin 1 receptor antagonist; interleukin 18; IL-18; prostaglandin E2; PGE2

Introduction

During the past three decades the United States and Western Europe, and also Asian countries, have witnessed a dramatic increase in the prevalence of obesity. Currently almost two-thirds of American adults (66.3%) are overweight; of these 32.4% are obese [1–3]. Obesity represents a major risk factor for diseases including diabetes, atherosclerosis and cardiovascular disease in which inflammation acts as a major driver in pathogenesis. Obesity is primarily considered a disorder of energy balance, and it was recently suggested that some forms of obesity are associated with chronic mild inflammation [4]. Many cytokines are systemically or locally elevated in obesity: they include interleukin 18 (IL-18) [5, 6], interleukin 1 (IL-1) [7, 8], interleukin 1 receptor antagonist (IL-1Ra) [20, 26, 27] and leptin [12]. Other inflammatory mediators also elevated in obesity include prostaglandin E2 (PGE2) [13] and C-reactive protein (CRP) [14, 15]. In this review we specifically focus on IL-1, IL-18 and PGE2, since both cytokines are known to activate the same transduction pathways but to have different actions on PGE2.

The induction and subsequent overproduction of proinflammatory cytokines, such as IL-1, TNF, and IL-6, is accompanied by increased production of their endogenous inhibitors, binding proteins and soluble decoy receptors [16–19]. For example, interleukin 1 receptor antagonist (IL-1Ra) is an anti-inflammatory cytokine that is also produced by white adipose tissue [20] and the pancreas [21] and that binds to the Interleukin 1 receptor (IL-1R) in competition with the proinflammatory cytokine interleukin 1 (IL-1) [22, 23]. The relative occupancy of the IL-1R1-IL-1Ra receptor complex with IL-1 agonist or with IL-1Ra determines whether the inflammatory signalling is "on" or "silenced" respectively [24, 25]. Systemic levels of the naturally occurring IL-1Ra have been shown to be elevated 3-8 fold in obese humans [20, 26, 27] and it has been suggested that this represents a protective response to the rise of the cytotoxic IL-1β in obesity. The critical balance between IL-1 agonists (IL-1α, cell bound and IL-1β, circulating) and IL-1Ra also plays an important role in susceptibility to and severity of many acute and chronic diseases, including obesity and diabetes [28–30], psoriasis [31], acute phase syndrome sepsis [32], fever [33–35], seizures [36] and stroke [37].

Many animal models have been developed...
with the aim of studying the mechanisms by which obesity may develop into insulin resistance and eventually into type 2 diabetes, including the role of inflammation in this progression. The severity of the diabetic phenotype in mice is sensitive to the genetic background [38, 39], and the inflammatory responsiveness of different mice strains varies widely [40]. Although glucose tolerance and insulin resistance can be modelled in mice, they do not develop a diabetic state that truly reflects the severity of the human diabetic condition. Glucose tolerance and insulin resistance tests are performed routinely in mice as an indicator of the development of diabetic phenotypes, but the reproducibility in these tests [41, 42] varies widely. With these caveats we proceed to summarise the present data.

**Interleukin-1 signalling**

IL-1 signalling involves the type I IL-1R (IL-1R1), a Toll-like receptor [43, 44] that heterodimerises with the IL-1R accessory protein (IL-1RACP) (figure 1) [45, 46]. There is a second IL-1R called IL-1R2, which is a soluble decoy receptor that is not thought to participate in signalling [47, 48]. Interleukin 1 beta (IL-1β) binds to the IL-1R1/IL-1R1AcP heterodimer which then initiates the signalling cascade resulting in the translocation of the transcription factor nuclear factor-kappa B (NF-κB) into the nucleus, where it induces the transcription of pro- and anti-inflammatory genes including inducible nitric oxide synthetase (iNOS), interleukin 6 (IL-6), IL-1Ra and cyclooxygenase-2 (COX-2), [49–51]. COX-2 catalyses the conversion of arachidonic acid (AA) to prostaglandin H₂ (PGH₂). PGH₂ is converted into prostaglandin E₂ (PGE₂) by terminal PGE synthase (PGES). PGE₂ signals through four different G-protein coupled receptors, EP1R–EP4R [52, 53], each of which has multiple splice variants with different signalling properties [54].

**Figure 1**
An overview of interleukin-1 NF-κB-dependent signalling. IL-1β binds to the IL-1R1/IL-1R1AcP heterodimer and the adapter protein myeloid differentiation primary response gene 88 (MyD88) is recruited to the complex [117]. The bound MyD88 recruits IL-1R-associated kinase-4 (IRAK4), which initiates the recruitment of Toll-interacting protein (Tollip) / IL-1R-associated kinase-1 (IRAK1) complexes [118]. IRAK4 phosphorylates IRAK1 and TNF-associated factor 6 (TRAF6) forms a complex with IRAK1 that subsequently associates with and activates the TGF-activated kinase 1 (TAK1). Disassociation of the IRAK-1/TRaf6 complex from the IL-1R and subsequent ubiquitination of Tab1 leads to the activation of the kinase TAK1, resulting in the phosphorylation of IkB kinase (IKK) [119]. Activation of the IKK complex leads to ubiquitination and proteasomal degradation of the inhibitory proteins IkB, and thus NF-κB transcription factor translocates into the nucleus where it induces the transcription of pro- and anti-inflammatory genes including inducible nitric oxide synthetase (iNOS), interleukin 6 (IL-6), IL-1Ra and cyclooxygenase-2 (COX-2) [49–51].
Knockout mice in studies on IL-1 signalling

Knockout mice have been essential in determining the role of IL-1 signalling in inflammation as well as the metabolic effects of a loss of IL-1 signalling (see table 1). IL-1R1 deficient mice (IL-1R1−/−) on a C57BL/6 background fed a normal chow diet exhibit mild late-onset obesity from approximately 5–6 months of age. Their increased body weight is due to increased fat mass and is accompanied by insulin resistance and decreased glucose tolerance [55]. IL-1β deficient mice fed normal chow have been reported not to develop obesity (up to 8 months) [56]. However, the combined deficiency of both IL-1β and IL-6 (IL-1β−/−, IL-6−/−) in double transgenic mice on a C57BL/6 background fed normal chow leads to early onset obesity at 10 weeks of age [56] while deficiency in IL-6 alone (IL-6−/−), on a C57BL/6 background leads to late-onset obesity by 6 months of age [57]. These results indicate that IL-1 and IL-6 are both involved in the regulation of body fat in what appears to be a redundant manner in young mice. Conversely, IL-1-Ra deficient mice (IL-1-Ra−/−) have been shown to exhibit a leaner phenotype compared to wildtype (WT) mice [58, 59], further supporting the idea that an intact IL-1 system is important for maintaining energy homeostasis. It should be noted that IL-1Rα mice have chronic inflammation and that IL-1, which occupies the IL-1R1 in the absence of IL-1Ra, suppresses appetite acutely as described in IL-1 induced “sickness syndrome” [60]. In addition, the lean phenotype may reflect aberrant lipid metabolism in these transgenic mice [58].

Table 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1R1−/−</td>
<td>Obesity at 5–6 mths, insulin resistance and glucose intolerance in mice on a C57BL/6 background.</td>
<td>[55]</td>
</tr>
<tr>
<td>IL-1β−/−</td>
<td>Normal weight up to at least 8 mths</td>
<td>[56, 121]</td>
</tr>
<tr>
<td>IL-1α−/−</td>
<td>Mice develop normally</td>
<td>[122]</td>
</tr>
<tr>
<td>IL-1αβ−/−</td>
<td>Mice develop normally</td>
<td>[122]</td>
</tr>
<tr>
<td>IL-6−/−</td>
<td>Obesity at 6 mths, insulin resistant and glucose intolerant</td>
<td>[57]</td>
</tr>
<tr>
<td>IL-1β−/−/IL-6−/−</td>
<td>Obesity at 10 wks</td>
<td>[56]</td>
</tr>
<tr>
<td>IL-1Ra−/−</td>
<td>Lean phenotype due to abnormal lipid metabolism. Increased insulin sensitivity.</td>
<td>[58, 59]</td>
</tr>
<tr>
<td>IL-18−/−</td>
<td>Obese at 6 mths, insulin resistant and glucose intolerant</td>
<td>[87, 123]</td>
</tr>
<tr>
<td>COX-2−/−</td>
<td>COX-2−/− mice, but not COX-1−/− or COX-2−/− mice have been shown to develop obesity. Although COX-2 is an important enzyme catalysing PGE2 synthesis, altered PGE2 signalling has not been implicated in the development of obesity in these mice.</td>
<td>[66]</td>
</tr>
<tr>
<td>EP1R−/−</td>
<td>Obese by 5 mths, insulin resistant and glucose intolerant</td>
<td>[74]</td>
</tr>
</tbody>
</table>

Therapeutic potential of blockage of IL-1 signalling in the treatment of type 2 diabetes

A recent study by Larsen et al. [28] showed that blockade of the IL-1R with human recombinant IL-1Ra (Anakinra™) improved glycaemic control and beta-cell secretory function and reduced markers of systemic inflammation in obese and non-obese patients with established type 2 diabetes [28]. At 13 weeks, in the Anakinra™ treated group, the glycated haemoglobin level was 0.46 percentage points lower than in the placebo group (P = 0.03); C-peptide secretion was enhanced (P = 0.05), and there were reductions in the ratio of proinsulin to insulin (P = 0.005) and in levels of IL-6 (P <0.001) and C-reactive protein (P = 0.002). A similar study in diet-induced obese mice also demonstrated the pancreas-protective effects of IL-1Ra administration, and presented evidence on improved beta cell survival and function with improved glucose tolerance [30].

An alternative therapeutic strategy for protection of the pancreas against the proinflammatory cytotoxic action of IL-1 in obesity involves the use of a high affinity monoclonal antibody to IL-1β [29]. Endogenous IL-1β is thereby sequestered in an antigen-antibody complex, shifting the balance at IL-1R in favour of the antagonist IL-1Ra. The strategy of immunoneutralisation of IL-1β by a high-affinity antibody represents an effective approach to improvement of glucose control in obesity in which the agonist is removed from the IL-1 receptor rather than relying on a sufficient excess dose of the lower affinity IL-1Ra antagonist to competitively block IL-1β-mediated occupancy and activity. Approximately a 20–100-fold excess of IL-1Ra over IL-1β is necessary to block the effects of IL-1β on pancreatic islets [8, 61]. As obesity develops, IL-1β is elevated in hyperglycaemic
beta cells and thus very large quantities of IL-1Ra are necessary to compensate for this rise [8, 21].

The IL-1β antibody has recently been shown to have significant therapeutic effects in the prevention of diabetes-related traits by improving glucose control and beta cell function in hyperglycaemic mice with diet-induced obesity [29]. After 13 weeks of treatment, the IL-1β antibody-treated group showed significantly reduced glycated haemoglobin (P = 0.049), reduced serum levels of proinsulin (P = 0.015), reduced levels of insulin and smaller islet size (P = 1.65E-13) relative to the control antibody-treated group. Neutralisation of IL-1β also significantly reduced serum amyloid A (SAA), indicating inflammation-induced acute phase response (P = 0.024). While there was no improvement in weight gain, a significant improvement of glycaemic control and of beta cell function is achieved by this pharmacological treatment, which may slow/prevent disease progression in type 2 diabetes. The mouse studies also provided insights into the cellular and molecular mechanisms involved in IL-1β cytotoxicity, allowing morphological examination of the pancreatic islet sizes and other parameters not easily followed in human patients in the absence of biopsy [28].

IL-1α is mostly cell-bound, but it potentially contributes to IL-1R1-mediated cytotoxicity in the pancreas [62]. Osborn et al. [29], using an IL-1β selective antibody, therefore showed that significant improvement of glycaemic control can be achieved by neutralisation of the soluble IL-1β alone, without blocking the action of IL-1α. The results suggest that the majority of IL-1R-mediated cytotoxic effects in the pancreas involve IL-1β. Because IL-1β is also a key mediator of impaired function and destruction of pancreatic beta cells during the development of type 1 diabetes [8, 63], an anti-IL-1β antibody may have therapeutic potential not only in the treatment of type 2 diabetes, but also in other forms of diabetes where tight glucose control is essential to prevent induction of IL-1β and further beta cell destruction. The collective results validate the therapeutic potential of blocking IL-1 signalling for the treatment of diabetes.

**EP3**

IL-1β stimulates the production of prostaglandin E2 (PGE2) primarily by transcriptionally up-regulating COX-2 through the action of the transcription factor NF-kB (figure 2) [64, 65]. Heterozygous COX-2+/− mice, but not COX-1−/− or COX-2−/− mice have been shown to develop obesity [66]. Although COX-2 is an important enzyme catalysing PGE2 synthesis, altered PGE2 signalling has not been implicated in the development of obesity in these mice. However, PGE2 has been implicated in human obesity, in which elevated circulating levels of PGE2 have been observed [13]. PGE2 is a lipid mediator with effects in the CNS including activation of the hypothalamic-pituitary-adrenal (HPA) axis [67] and febrile response [68]. PGE2 signalling is also an important component of inflammation [69–71]. PGE2 has also been shown to inhibit lipolysis in WAT and stimulate the secretion of leptin, suggesting that PGE2 signalling is important for body weight homeostasis [72]. PGE2 can signal through four different G-protein coupled receptors, EP1R–EP4R [52, 53]. The EP subtypes exhibit differences in signal transduction, tissue localisation and regulation of expression (for review see [73]).

Mice that lack the prostaglandin receptor EP3R develop an obese phenotype and have a significantly higher body weight than WT littermates from 10 weeks of age when fed normal chow [74]. By 30 weeks of age, EP3-deficient mice weigh on average >30% more than their WT littermates. Obesity in EP3R−/− mice is characterised by elevated leptin and insulin levels, increased abdomi-
nal and subcutaneous fat and increased liver weight. EP3R<sup>−/−</sup> mice exhibit increased motor activity during the light cycle but this is not sufficient to offset their increased feeding frequency during this phase, leading to obesity. PGE2 has been reported to be a somnogenic agent [75], and it has therefore been suggested that EP3R deficient mice do not stabilise sleep and may wake up more easily. This sleep deficit may explain why EP3R-deficient mice exhibit increased food consumption during the light cycle. These observations expand the roles of prostaglandin E2 signalling in metabolic regulation beyond the reported stimulation of leptin release from adipose tissue, to involve CNS actions mediated by EP3R in feeding behaviour and the regulation of sleep architecture.

### IL-18

IL-1β is closely related to and shares a very similar three dimensional protein structure with the cytokine interleukin 18 (IL-18) [76, 77]. Both the IL-1 receptor and IL-18 receptor belong to the Toll/IL-1R (TIR) superfamily which is defined by a common intracellular TIR domain, involved in the initiation of signalling [78]. The IL-18 receptor (IL-18R) complex is composed of the interleukin 18 receptor (IL-18R) to which IL-18 binds [77], and by the IL-18 receptor accessory protein (IL-18RAP). The IL-18 binding protein (IL-18BP) is a constitutively secreted protein which binds to IL-18 and functions as a decoy to prevent the initiation of signal transduction at the IL-18 receptor [79]. Transgenic mice that express the human form of the IL-18BP isoform α (IL-18BP-Tg), which binds with high affinity to IL-18 [80], show that high levels of IL-18BP effectively neutralise IL-18 and can protect against inflammatory stimuli.

In addition to structural features, IL-18 and IL-1 share some common signalling pathways (figure 3). Binding of IL-18 to the IL-18R is followed by recruitment of the IL-1 receptor activating kinase (IRAK) [81, 82] via the adapter MyD88 [83] in a similar way to that described in figure 1, culminating in the translocation of NF-κB to the nucleus [82, 84].

Engagement of the IL-18R complex also activates the mitogen-activated protein kinase (MAPK) p38, JNK and ERK through both IRAK and STAT3 [85–89]. It is noteworthy that while IL-18 and IL-1 share some common signalling pathways, their effects on COX-2 induction are different. IL-18, unlike IL-1, does not induce COX-2 and PGE2 production in the cell types studied. PGE2 concentration can however be affected by the Interleukin 18 binding protein (IL-18BP), as in vitro experiments have shown [90]. IL-18 is implicated in the pathogenesis of several diseases including atherosclerosis, ischaemic heart diseases, infection, cancer [91–95], and more recently a novel function for IL-18 in the control of energy homeostasis has also been described [87, 96]. Serum levels of IL-18 directly correlate with body mass index, adiposity and insulin resistance, and circulating levels of IL-18 are elevated in obesity [5, 6, 97]. Fat-resident monocyte/macrophage lineage cells are major sources of IL-18 [4], and adipocytes from obese humans secrete three times more IL-18 than those from lean donors [98]. Subcutaneous adipose tissue IL-18 mRNA is also elevated in human obesity, correlating with insulin resistance [99]. The results suggest an adipocytokine-like action of IL-18 in obesity.

Studies in mice which lack IL-18 (IL18<sup>−/−</sup>) or the α component of its receptor (IL18R<sup>−/−</sup>) have revealed that IL-18 signalling modulates food intake, metabolism, and adiposity during adulthood [87, 96]. Both male [87] and female [96] IL18<sup>−/−</sup> mice develop obesity by approximately 6 months of age when fed normal chow. IL-18 administered centrally or peripherally suppresses appetite, feed efficiency, and weight regain in food-deprived C57BL/6J mice in both sexes [96] without inducing fever or malaise-like behaviour such as the “sickness syndrome” caused by IL-1 (Dantzer 2001). Furthermore, IL-18 deficiency leads to hyperphagia before the onset of overweight, decreased energy expenditure in females and in-
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The IL-1 system has important roles in the brain and periphery. Insulin resistance is linked to increased respiratory exchange ratios (volume of carbon dioxide production [VCO₂]/volume of oxygen consumption [VO₂]) in mutants of both sexes. Adult IL-18⁻/⁻ mice gained 2–3 times more weight than WT mice per unit energy consumed of low or high fat diet. IL-18⁻/⁻ mice showed 2–3 times greater whole-body adiposity than that of WT with the most significant differences in gonadal, mesenteric, and inguinal depots [96]. Together the data suggest that endogenous IL-18 signalling modulates food intake, metabolism and adiposity during adulthood in male and female mice in a manner that opposes positive energy balance. The results also indicate the possibility of both central and peripheral targets for IL-18 to control energy homeostasis.

**Table 2**
The IL-1 system has important roles in the brain and periphery.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Acute effects (fever and anorexia) mediator of leptin action</td>
<td>[22, 123]</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipolysis</td>
<td>[124, 125]</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin secretion and beta cell apoptosis</td>
<td>[115, 126–128]</td>
</tr>
<tr>
<td>Liver</td>
<td>Induces IL-1Ra</td>
<td>[20]</td>
</tr>
</tbody>
</table>

**Perspective**

Cytokine receptors are expressed on a wide range of peripheral cell types in different tissues, such as, among others, white adipose tissue (WAT) [100, 101], pancreas [8, 102] and muscle [103] (see table 2). WAT produces both IL-1β and IL-1Ra and expresses IL-1R1, IL-1R2, and IL-1R1AcP, indicating that adipose tissue is capable of functional IL-1 signalling [16, 20, 26]. WAT expression of IL-1Ra and IL-1R1 is up-regulated in obesity, providing further evidence in favour of dysregulated IL-1 signalling in obesity [20]. However, cytokine receptors have also been found to be expressed on specific neuronal populations such as hippocampal neurons and neurosecretory cells in the hypothalamus [104–106], as well as on microglia and astrocytes [107–109]. Due to the widespread expression of cytokine receptors in both the brain and the periphery, it is difficult to pinpoint where cytokines such as IL-1β or IL-18 exert their effects on body weight. Since these obese, cytokine-deficient mice lack cytokine signalling both in the brain and in the periphery, it is impossible to determine the specific sites of action using the transgenic tools currently available. However, the field is still young, and with the development of tissue-specific knockouts and directed viral vectors [110–112] it should be possible in future studies to differentiate the central and peripheral effects of these cytokines on body weight homeostasis.

The mouse studies quoted here present a paradox, since in general pro-inflammatory cytokine-deficient mice are obese (e.g. IL-1R⁻/⁻, EP3⁻/⁻, IL-18⁻/⁻), but elevation of these cytokines is observed systemically in obesity. A possible explanation is that the elevated levels of inflammatory mediators could lead to a state of resistance analogous to that which occurs with the adipocytokine leptin, where there is actually less inflammatory signalling in obese individuals despite elevated circulating cytokine levels. The lean phenotype of IL-1Rα⁻/⁻ mice needs to be mentioned for the sake of completeness, but it is noteworthy that these animals are very sick and multiple processes may account for their inability to gain weight similarly to WT mice littermates.

With the rapid expansion of obesity research many genetic factors involved in obesity that contribute to the phenotype are being described, along with the important social factors. While the influence of cytokines certainly pales in comparison to leptin [113, 114], cytokines may be important in contributing to obesity, which affects the vast majority of people with high BMIs. The recognition of obesity as a risk factor for type 2 diabetes also increases the importance of understanding the contribution of cytokines in the transition from obesity to type 2 diabetes. In this context, the cytotoxicity of IL-1 receptor agonist for the pancreatic beta cells and the inhibitory effects on the beta cells’ ability to respond to elevated glucose become important [115]. While anti-IL-1 therapies may not affect body weight, they may protect the pancreatic beta cells that are stressed in obese individuals by increased insulin demand and elevated circulating pro-inflammatory cytokines.

Since IL-1ra (Anakinra™) is already approved for the rheumatoid arthritis indication and anti-IL-1β antibodies are in clinical trials, future clinical trials to protect the pancreas in obese subjects will rapidly follow. The consequences of diabetes are so devastating that if anti-IL-1 therapy is successful in preventing or slowing conversion of obesity to type 2 diabetes it is likely that such therapy will be widely used, especially as the anti-IL-1 biologicals appear to be safe.

The selective suppression of EP3R-mediated PGE2 signalling has not been studied in humans, and the widely used COX-1 and COX-2 inhibitors reduce the PGE2 agonist concentration at all prostanoid receptor subtypes simultaneously. As soon as a selective, CNS active EP3R antagonist becomes available, it will certainly be put to the proof of concept studies in obesity.
Transgenic IL-18BP mice have shown that high levels of IL-18BP effectively neutralise IL-18 and can protect against inflammatory stimuli [80]. These transgenic mouse studies have prompted further investigation into the effects of recombinant IL-18-BP (Takedinig-α®) which is currently in phase I clinical trials for Crohn’s disease and rheumatoid arthritis [116]. Preclinical studies suggest that the IL-18 system may affect body weight homeostasis at several levels, but pharmacological exploitation of the appetite- and energy metabolism-suppressing effects of IL-18 signalling awaits clinical experimentation on obese and diabetic subjects.

These mouse studies highlight potential new therapeutic targets in the field of obesity and diabetes. The paradoxical findings that pro-inflammatory cytokine-deficient mice are generally obese, while systemic elevation of these cytokines is observed in obesity, suggests that disruption of the homeostatic balance of cytokines in either direction is detrimental, and that moderate inhibition of pro-inflammatory mediators using pharmacological inhibitors is likely to have therapeutic effects.

Correspondence:
Professor Tamas Bartfai
The Harold L. Dorris Neurological Research Institute
The Scripps Research Institute
10530 N Torrey Pines Rd.–SR307
La Jolla, CA 92037
USA
btbartfai@scripps.edu

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